## REMARKS

By the present communication claim 1 has been amended; claim 15 has been canceled without prejudice or disclaimer; and no claims have been added. Claim 4 was previously canceled. Claims 7 and 14 have been withdrawn from further consideration. The amendments do not raise any issues of new matter being fully supported by the specification and claims as filed. Support for the amendments to claim 1 may be found, for example, in the specification at paragraph [0067]. Accordingly, upon entry of the present amendment, claims 1-3, 5-6 and 8-13 will be under consideration.

**Rejections under 35 U.S.C. §112, Second Paragraph**

Applicant respectfully traverses the rejection of claims 1-4 under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to recite requisite steps necessary to practice the invention. Applicant notes that claim 4 was previously canceled rendering the rejection moot as to such claim.

Specifically, the Office Action alleges that the claims fail to recite a direct administration step. Without acquiescing to the reasoning offered in the Office Action, Applicant has amended claim 1 as follows:

> A method for suppressing pathological calcification of the meniscal and articular cartilage matrix, comprising: administering to a subject in need thereof an inhibitor of activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes in the cartilage matrix, wherein the inhibitor is A20 or NG-monomethyl-L-arginine acetate (NMMA), thereby suppressing pathological calcification in the cartilage matrix in the subject.

Indefiniteness analysis requires whether those skilled in the art would understand what is claimed when read in light of the specification (see, e.g., *Morton International, Inc. v. Cardinal Chemical Co.*, 28 U.S.P.Q.2d 1190 (Fed. Cir. 1993)). Applicant directs the Office's attention to

paragraph [0067] of the specification which discusses how the inhibitor is to be administered to a subject. Paragraph [0067] recites as follows:

> The inhibitor of the methods of the invention can be delivered orally, intravenously, intraperitoneally, intramuscularly, subcutaneously, intranasally, and intradermally, as well as, by transdermal delivery (e.g., with a lipid-soluble carrier in a skin patch placed on skin), or even by gastrointestinal delivery (e.g., with a capsule or tablet). Furthermore, inhibitors used in the methods of the present invention in certain aspects are delivered directly to a site of chondrocyte matrix calcification., such as for example, directly to a joint, such as an arthritic joint. The dosage will be sufficient to provide an effective amount of an inhibitor either singly or in combination, as discussed above. Some variation in dosage will necessarily occur depending upon the condition of the patient being treated, and the physician will, in any event, determine the appropriate dose for the individual patient. The dose will depend, among other things, on the body weight, physiology, and chosen administration regimen.

In light of the amendments to claim 1 and the adequate disclosure of how the inhibitor of the claimed invention is to be administered or delivered to a subject, Applicant respectfully submits that one of skill in the art would clearly understand how the inhibitor is to be administered to the cartilage matrix. The specification discloses multiple delivery means including direct delivery, as well as indirect delivery means. Additionally, paragraphs [0068]-[0069] disclose various dosage forms for various delivery methods. Applicant respectfully submits that the claims are not indefinite because one skilled in the art, at the time the application was filed, would understand the metes and bounds of the subject matter of the Applicant's invention as well as how the inhibitor is contemplated to contact the cartilage matrix.

Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §112, second paragraph, as allegedly being indefinite.

**Rejections under 35 U.S.C. §103**

Applicant respectfully traverses the rejection of claims 1, 2, 3, 5, 6 and 8-13 under 35 U.S.C. §103(a) as allegedly obvious over Nurminskaya et al., in view Hashimoto et al., and further in view of Heyninck et al.

The recent U.S. Supreme Court decision in the *KSR International v. Teleflex Inc.* (82 USPQ2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the KSR rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations.

The Office Action relies on Nurminskaya as allegedly teaching that expression of transglutaminase (tTGase) and zymogen factor (FXIIIa) is unregulated in chondrocyte hypertrophy and calcification and that these factors are implicated in apoptotic cell death mechanisms in chondrocytes. The Office Action concedes that the reference does not specifically teach that blocking activation or activity of tTGase and FXIIIa would decrease apoptosis in pathological states (Office Action, page 5). The Office Action relies on Hashimoto as allegedly disclosing that articular cartilage matrix calcification and degradation are implicated in human osteoarthritis. Hashimoto also allegedly discloses that "future treatment options" (*e.g.*, apoptotic inhibitors) would alleviate chondrocyte apoptosis. The Office Action relies on Heyninck as allegedly teaching that cellular expression of A20 inhibits TRAF2 mediated NF-κB signal transduction and that such pathway is implicated in apoptosis.

In the prior response mailed August 12, 2007, Applicant presented arguments that the Office failed to establish a *prima facie* case of obviousness under the 3 basic criteria of *KSR*. Applicant reasserts all such arguments on the record. In response, the Office Action asserts that under *KSR,* an additional rationale for the finding of obviousness is that the claims would have

been obvious because a person of ordinary skill in the art has good reason to pursue the known options within his/her technical grasp. Accordingly, based on the alleged prior art teachings, the Office Action concludes that the skilled artisan would have known that inhibiting tTGase and FXIIIa mediated NF-κB signal transduction to reduce apoptosis would alleviate disorders of pathological calcification and degradation of the cartilage matrix and that it would have been obvious for one of skill in that art to try administration of A20 to treat such disorders and to identify agents that affect matrix calcification because the artisan has good reason to pursue the known options within his or her technical grasp.

Applicant respectfully submits that use of A20 as an inhibitor to suppress pathological calcification in the cartilage matrix was not a known option within the artisan's technical grasp. Heyninck's alleged disclosure of A20 as an inhibitor of TNF-induced NF-κB activation would not lead one of skill in the art to conclude that A20 would effectuate inhibition of apoptosis in chondrocytes. Heyninck discusses the complexity of TNF-induced activation of the NF-κB signal transduction cascade, disclosing that A20 is itself under the control of NF-κB activation (page 1479, column 1, paragraph 1). Additionally, Heyninck discloses that NF-κB signal transduction is cell-type dependent and implicates a variable role of A20 in different cell types. For example, the authors disclose that "stable expression of A20 has been reported to be unable to prevent TPA-induced NF-κB activation in breast carcinoma MCF cells" (page 1479, column 2, last paragraph). From the disclosure of Heyninck, the skilled artisan would conclude that induction of apoptosis is cell-type dependent and inhibition of NF-κB activation is dependent on how NF-κB activation is induced.

Additionally, the Applicant directs the Office to Exhibits 1-5, submitted herewith, to show that it is well settled in the art that the induction of apoptosis, as well as inhibition thereof, is cell type dependent. (see generally, the Introduction of Exhibit 1 (Zhang et al., *Journal of Biological Chemistry* (Nov. 2007)) discussing the cell type dependent induction of apoptosis by cAMP levels;

page 304 of Exhibit 2 (Lecureur et al., *Oncogene*, 20:303-313 (2001)) discussing cell-type dependent induction of apoptosis by p53 levels; the Introduction of Exhibit 3 (Hao et al., *Cancer Research*, 64:3607-3616 (2004)) discussing the cell-type dependent requirement of BAX activation in TRAIL-induced apoptosis; the Introduction of Exhibit 4 (Munger et al., *PNAS*, 98:10410-10415 (2001)) discussing that the mechanism of viral induction of apoptosis is cell-type dependent; and the Introduction of Exhibit 5 (Zou et al., *Develop Growth Differ*, 42:257-264 (2000)) showing that IFN-γ-mediated apoptosis is cell type dependent.

In light of the disclosure of Heyninck and knowledge in the art, the skilled artisan would not have known how apoptosis is induced in chondrocytes and how to inhibit apoptosis in such a cell. Accordingly, Applicant asserts that use of A20 as "an inhibitor of activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes in the cartilage matrix" to suppress pathological calcification in the cartilage matrix, as recited in the pending claims, was not a known option within the artisan's technical grasp.

With regard to claim 11, directed to a method of identifying an agent that inhibits matrix calcification, Applicant respectfully asserts that such a method was not a known option within the artisan's technical grasp. Claim 11 recites as follows:

> A method for identifying an agent that inhibits matrix calcification, comprising contacting a chondrocyte *in vitro* with a test agent under conditions for inducing matrix calcification, wherein the chondrocyte expresses zymogen factor XIIIa (FXIIIa) and/or tissue transglutaminase (tTGase); and determining the effect of the test agent on activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes of the cartilage matrix, wherein inhibition of activation and/or activity is indicative of a test agent that inhibits matrix calcification.

None of the cited references disclose or even hint at an *in vitro* method of identifying inhibitors of matrix calcification, by determining a test agent's effect on the activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes of the cartilage

matrix. Relying on the cited art, a skilled artisan would not have known whether inhibition of activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes of the cartilage matrix would inhibit matrix calcification. None of the cited references clearly establish such an association beyond conjecture. Accordingly, Applicant submits that development of the screening assay of the pending claims was not a known option within the artisan's technical grasp.

For the aforementioned reasons, Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. §103(a).

Applicant respectfully traverses the rejection of claim 2 under 35 U.S.C. §103(a) as allegedly obvious over Nurminskaya et al., in view of Hashimoto et al., further in view of Heyninck et al. and Gohr et al.

Applicant notes that claim 2 is dependent on claim 1 and further limits the method of claim 1 by reciting that "the inhibition of activation is accomplished by blocking production of a member selected from the group consisting of interleukins IL-I, IL-8, nitric oxide donor Noc-12, peroxynitrite generator Sin-1, tumor necrosis factor α (TNFα), and S100 family of proteins." For the reasons presented above in support of the non-obviousness of claims 1, 5 and 11, Applicant respectfully asserts that use of A20 as an inhibitor of activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes in the cartilage matrix to suppress pathological calcification in the cartilage matrix was not a known option within the artisan's technical grasp. Accordingly, use of A20 or NMMA to inhibit activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes in the cartilage matrix through the blocking of production of S100 family of proteins is likewise non-obvious.

For the aforementioned reasons, Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. §103(a).

Applicant respectfully traverses the rejection of claim 15 under 35 U.S.C. §103(a) as allegedly being unpatentable over Nurminskaya, in view of Hashimoto, and further in view of Studer, et al. Applicant has canceled claim 15 rendering the rejection moot.

**Conclusion**

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

No fee is deemed necessary with the filing of this paper. However, if any fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

Date: February 21, 2008

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